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Review

Nanoparticle-mediated drug delivery system for atherosclerotic cardiovascular disease

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ABSTRACT

Administration of drugs and other therapeutic agents has been the central strategy of contemporary medicine for cardiovascular disease. The use of drug delivery systems (DDS) includes micelles, liposomes, polymeric nanoparticles, dendrimers, carbon nanotubes, and crystalline metals. Nano-DDS modify in vivo drug kinetics, depending on (patho)physiological mechanisms such as retard excretion, vascular permeability, and incorporation by mononuclear phagocyte systems, which constitute the 'passive-targeting' property of nano-DDS. These properties of nano-DDS are applicable to inflammatory diseases including atherosclerosis. Atherosclerotic plaque destabilization and rupture account for the majority of acute myocardial infarction, for which inflammatory monocytes and macrophages play critical roles. In our experience, polymeric nanoparticles have been delivered to inflammatory monocytes and macrophages in an atherosclerotic mouse model. Nano-DDS loaded with pioglitazone reduced $Ly6C^{high}$ inflammatory monocytes and increased $Ly6C^{low}$ non-inflammatory monocytes in the peripheral blood, and induced M2 macrophage-associated genes in the aorta. Pioglitazone-nanoparticles finally stabilized atherosclerotic plaques assessed by a decrease in the number of buried fibrous caps in the plaque. Application of nano-DDS is a unique and promising approach to prevent life-threatening cardiovascular events including acute myocardial infarction by regulating inflammation in the cardiovascular system.

Contents

Nanoparticle-mediated drug delivery systems

Administration of drugs and other therapeutic agents has been the central strategy of contemporary medicine, based on the concept that a certain disease comprises diseased cells and their molecules within healthy organs and body. Even upon deep understanding of the mechanisms of disease development and therapeutic targets, drugs need to overcome physiological barriers,

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namely circulation to organs, and tissue to cells, to reach therapeutic targets. From another aspect, any drugs possess potential toxicity that may limit their safety dose and thereby therapeutic efficacy. Targeting drugs to diseased organs/cells may reduce potential adverse effects; therefore, the use of drug delivery systems (DDS) enhances the efficacy and safety of therapeutic agents.

The recent application of nanotechnology to medicine has developed nanoparticle-mediated DDS (nano-DDS), which modifies in vivo kinetics of the therapeutic and diagnostic agents. One of the most important motives for nano-DDS is drug targeting, which may utilize physiology and pathophysiological properties unique to certain disease processes [1]. Nano-DDS can be composed of a variety of materials and structures, including lipids to form micelles or liposomes [2], polymers [3–5], dendrimers [6], carbon nanotubes, and metallic nanoparticles such as crystalline iron oxide and gold nanoparticles [7] (Fig. 1). Here we describe selected examples of nano-scale materials tested as nano-DDS. Micelles are formed from lipids and other amphiphilic artificial molecules such as polymers. Micelles self-assemble in aqueous solution and may incorporate hydrophobic therapeutic agents to overcome solubility problems. The size (usually 10–100 nm in diameter) and the enclosed space are more confined to those of liposomes (Fig. 1A). Liposomes mainly consist of phospholipids that form bilayers with an aqueous phase inside, and are heterogeneous in size, often ranging from a few hundreds to thousands of nanometers in diameter. Liposomes are the most extensively tested nano-DDS in basic and clinical medicine with United States Food and Drug Administration (FDA) approval. Chemicals, nucleotides, and also crystalline metals are incorporated in liposomes (Fig. 1B). Currently, two FDA-approved polymers, polylactide (PLA) and poly(lactide-co-glycolide) (PLGA), are widely used for the synthesis of polymeric biodegradable nano-DDS. PLGA polymers incorporate hydrophilic and hydrophobic therapeutic agents including chemicals and nucleotides by emulsion solvent diffusion methods, and are being tested for intractable diseases including cardiovascular disease (Fig. 1C). Dendrimers are highly branched macromolecules with controlled near monodisperse three-dimensional architecture emanating from a central core. Polymer growth starts from a central core molecule and growth occurs in an outward direction by a series of polymerization reactions, which determines the size of dendrimers starting from a few nanometers. Cavities in the core structure and folding of the branches create cages and channels for the incorporation of therapeutic agents (Fig. 1D) [6]. Carbon nanotubes belong to the family of fullerenes and consist of graphite sheets rolled up into a tubular form. The diameter and the length of single-walled nanotubes may vary between 0.5–3.0 nm and 20–1000 nm, respectively [8]. Therapeutic agents are attached on either the inner or outer tube wall surfaces, which are the so-called filling or wrapping modes of binding, respectively (Fig. 1E). In contrast, metallic nanoparticles are functional themselves. Ion oxides are usually prepared as alkaline co-precipitations of Fe^{2+} and Fe^{3+} salts in water in the presence of a suitable hydrophilic polymer such as dextran or poly(ethyleneglycol). This yields an iron core of 4–5 nm in diameter, which is hexagonally shaped and surrounded by dextran or poly(ethyleneglycol) molecules to form superparamagnetic iron oxide particles (60–150 nm) as contrast agents for magnetic resonance imaging [7,9,10]. Gold nanoparticles possess a unique photodynamic property by absorbing near-infrared lights and emitting lights and heats, which has been tested for a cancer photothermal therapy. Also, gold nanoparticles are conjugated with various therapeutic agents and targeting moieties, and act as drug carriers (Fig. 1F) [1]. Intravital kinetics of nano-DDS may be diverse; their behavior within the biological environment is affected not only by size, but also by their chemical make up and morphology. However, the most important determinant of the physiological behaviors of nano-DDS is the size, as discussed below.

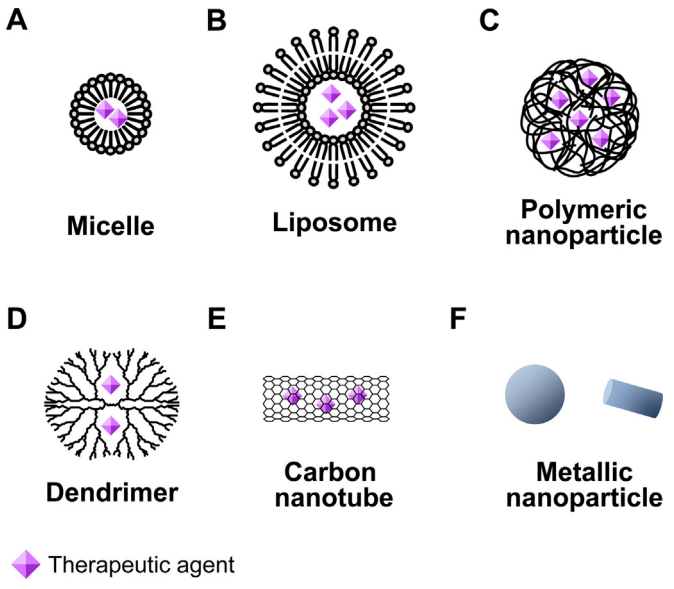

Fig. 1. Schematic description of nanoparticle mediated drug delivery systems. (A) Micelle self assembles from lipids or synthetic macromolecules with hydrophilic heads and hydrophobic tails in an aqueous solution. Placing hydrophobic tails inside, lipid micelles encapsulate hydrophobic therapeutic agents. (B) Liposome is composed of lipid bilayer. Placing hydrophilic heads outside and inside, liposomes encapsulate hydrophilic solution and therapeutic agents inside. (C) Polymeric nanoparticle, formed from an assembly of macromolecular polymers, containing therapeutic agents. (D) Dendrimer, composed of macromolecular polymer incorporating therapeutic agents within its structure. (E) Carbon nanotubes, a cylindrical structure of covalently bonded carbon atoms, can carry therapeutic agent inside. (F) Crystalline metals in nano-meter scale possess therapeutic or imaging function themselves.

Physiological behaviors of nano-DDS

Nano-sized materials (10–300 nm in diameter) tend to remain in circulation avoiding renal excretion, which is a primary feature of nano-DDS. While circulating in the blood stream, nano-DDS extravasates from the vasculature with enhanced permeability, such as angiogenic vessels in tumors, and vessels in organs after ischemia-reperfusion, which is an important mechanism that affects tissue distribution of nano-DDS [3]. Neovasculature in tumor lacks functional lymphatic vessels as well as enhanced vascular permeability, causing an accumulation of nano-DDS in the tumor microenvironment. This phenomenon is referred to as enhanced permeability and retention effects of nano-DDS [11]. Recognition and incorporation by the mononuclear phagocyte system (MPS, also known as the reticuloendothelial system), namely neutrophils, monocytes, and macrophages in the blood, liver, spleen, and lymph nodes is also a common physiological behavior for nano-DDS, which may affect the blood circulating time and tissue/cell distribution [12]. One of the first clinically approved nano-scale DDS therapies was a liposomal formulation of doxorubicin, a cytotoxic drug used for cancer chemotherapy. During its development, encapsulation of doxorubicin in liposomes prolonged blood half-life compared to the free drug, which was found unsatisfactory, because of the entrapment by MPS [13]. An addition of polyethylene glycol (PEG) to the surface of nano-DDS was shown to reduce the recognition of MPS, and in the case of doxorubicin liposome, the addition of PEG reduced